REMARKS

Status of the Claims

Claims 1-8, and 9-24 are pending.

Entry of the Above Amendment

Claims 22-24 are added in the above amendment. The claims do not add subject matter previously unconsidered by the Examiner, and they would not be a burden to examine at this time. Accordingly, entry of this amendment is respectfully requested.

Issues Under 35 U.S.C. § 112

Claims 1-8, 17, 18, and 21 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Section 112, first paragraph, states, *inter alia*: "The specification shall contain a written description of the invention." However, in order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same

terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." (citation omitted).

Significantly, the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented. Thus, it is only necessary that "the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at [the time of filing] of the later claimed subject matter".(citation omitted).

In the present case, it should be obvious that one of ordinary skill in the art would understand that "the terminology 4% or less of impurity products," as stated in the office action, and "impurities comprise at least one of a non-amphotericin B polyene compound or an endotoxin compound" was clearly possessed by the inventor as inventive subject at the time of filing the application.

With respect to the impurity percentage, Applicants respectfully submit that even if there is not word-for-word support for the language in the specification, one of ordinary skill in the art would clearly understand "greater than 96% pure" can be basically equated with, in scope and breadth, to "4% or less of impurity products." In fact, one of ordinary skill in the art would understand that they both can be readable on 100% purity. Since the support can be inherent, Applicants' respectfully submit that the claims are sufficiently supported to be compliant with § 112.

With respect to the "impurities comprising at least one of non-amphotericin B polyene compound or an endotoxin compound," Applicants respectfully submit that there is sufficient support in the specification for this limitation as well.

One of ordinary skill in the art would understand that the purified amphotericin B discussed in the specification is free from "other" polyenes in the described amounts. From a reading of the specification, one of ordinary skill in the art would understand that non-amphotericin B polyenes are considered impurities. Additionally, there are numerous examples in the specification discussing the present invention and purification from polyene compounds and/or endotoxins. See, for example, pages 10, 13, 15, and 18.

Furthermore, the Federal Circuit has repeatedly noted that the Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. That burden may be met with evidence that one skilled in the art would fail to "recognize in the disclosure a description of the invention defined by the claims." (citation omitted). The outstanding Office Action offers no objective evidence to offer a different view than the one provided above.

Accordingly, Applicant's respectfully submit that this rejection should be withdrawn.

Issues Under 35 U.S.C. § 103

Claims 1-8 and 17-21 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Lopez-Berenstein et al. (US '167) in view of US Patent No. 4,902,789 to Michel et al. (US '789),

or US Patent No. 4,308,375 to Tsang (US '375). This rejection is respectfully traversed.

As is clear from the record, the primary reference, US '167, fails to disclose or suggest the claimed purity features. As Applicants have previously stated, this reference fails to even address amphotericin B purity at all in the same terms as the present invention. US '167 is concerned with encapsulation. At col. 4, lines 8-19, achieving 100% encapsulation is discussed.

These deficiencies are not remedied by the secondary references.

US '789 discloses a four solvent system for purifying amphotericin B: methanol, dimethylformamide, methylene chloride, and water. However, purity is measured as a "residue on ignition" as a weight percentage (vs. a percentage of impurities for the present invention). As previously indicated, one of ordinary skill in the art would not expect to be able to extrapolate purity as measured by residue on ignition to the present application because many of the contaminants the present inventors identified as polyenes should still be present based on the residue on ignition measurement.

Said another way, Applicants respectfully submit that if the residue on ignition test was performed properly, any organic compound consisting of carbon, hydrogen, and nitrogen (which would include amphotericin B and other polyene contaminants) would be expected to ignite completely. Thus, under proper conditions, the residue remaining after ignition is an index of inorganic or metal content and not of purity of the organic material. Tremendous amounts of contaminant with similar "melting points" or "ignition points" could be present in a final product

that one would not want administered as a medication. Thus, Applicants respectfully submit that it is improper to assert the US '789 secondary reference on the basis that it provides motivation for an active ingredient that has at least 94% amphotericin B is not proper.

The other secondary reference, US '375, discloses a method of purifying amphotericin B with an ion exchange column that removes gram positive and gram negative bacteria. This reference does not address the polyene impurity issues that are addressed by the present invention. Thus, Applicants respectfully submit that it is also improper to assert that the US '375 secondary reference can be relied upon in combination with US '167.

Thus, the statement in the Office Action that "since purification of amphotericin B was well known in the art at the time the claimed invention was made as disclosed by [the secondary references]..." is not a correct interpretation of the references.

In view of the above, it is clear that the above references fail to present a *prima facie* case of obviousness. As stated in the previous response, in order to establish a case of obviousness, the prior art references, when combined, must also teach or suggest all the claim limitations. Also see M.P.E.P. §2142. In this case, the primary reference fails to disclose or suggest the claimed amphotericin B features of the claims. Furthermore, it is clear from the above that the secondary references fail to remedy or even suggest the deficiencies of the primary reference. Therefore, Applicants respectfully submit that the obviousness rejection should be withdrawn.

The Office Action states that "applicant has not provided any evidence in verified form

showing that the references' purification process would not result in a product having the claimed purification levels.

Applicants respectfully submit that requiring such evidence improperly shifts the burden of persuasion to the Applicants. Until the requirements for establishing a *prima facie* case of obviousness are met, there is no duty or need for the Applicants to present further evidence. Nonetheless, attached is a Declaration under Rule 132 that further addresses the issues precluding allowance raised in the office action.

The Office Action states that "it is generally acknowledged that it is desirable for the active component in pharmaceutical compositions to be as pure as possible..., so absent unexpected results relating to obtaining the subject compound having the claimed purity levels, the claimed methods of using said compound are prima facie obvious over the prior art."

Three cases routinely cited (including in M.P.E.P. § 2144.04) with respect to "purity" are *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966); *Ex parte Stern*, 13 USPQ2d 1379 (Bd. Pat. App. & Inter. 1987); and *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989).

In the *Cofer* decision, claims to a free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals. Applicants respectfully submit that the facts of the present case are comparable to those in *Cofer*. The prior art fails to disclose or suggest the claimed amphotericin

B compositions, including compositions that are free from non-amphotericin B polyene compounds or endotoxin compounds.

In the *Ex parte Stern* decision, claims to interleukin 2 purified to homogeneity were held unpatentable over references which recognized the desirability of purifying interleukin 2 to homogeneity in a view of a reference that disclosed a method of purifying proteins having molecular weights in excess of 12,000 to homogeneity. The prior art method was said to be similar to the method disclosed by appellant for purifying interleukin 2. Applicants respectfully submit that the facts of the present case are distinguishable from those of the *Stern* case. Here, there is no recognition of amphotericin purity, including with respect to compositions that are free from non-amphotericin B polyene compounds or endotoxin compounds. Additionally, as stated above, the "prior art methods" are not comparable to the instant purification methods or resulting products.

In the *Gray* decision, the invention involved human nerve growth factor beta-NGF identified by a particular amino acid sequence and free from other proteins of human origin. The prior art disclosed isolating human beta-NGF from placental tissue. In contrast, the present prior art references fail to discuss purification consistent with the claimed invention.

Finally, very recently the Federal Circuit addressed the subject of purity. *In Aventis Pharma Deutschland GMBH, et al. v. Lupin, LTD., et al.*, No. 06-1530-1555 (Fed. Cir. September 11, 2007), the Court addressed obviousness of a pharmaceutical compound in a

formulation "substantially free of isomers." There, the Court held that the 5(S) stereoisomer (using the labeling method of "R" and "S" for each stereocenter) of ramipril, in a form substantially free of other isomers, was obvious over the prior art because the prior art provided a sufficient reason to look to the 5(S) configuration. The court noted that "all of the stereocenters in the most therapeutically active stereoisomers of these prior art are in the S configuration." As in the *Gray* decision, the present prior art references fail to discuss purification consistent with the claimed invention. For example, none of the asserted prior art references address polyene/endotoxin impurities.

Interestingly, the Federal Circuit discussed circumstances comparable to the present case when mentioning situations where the *Aventis* decision may have gone the other way. For example, the Court stated that "for example, it may not be known that a purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight itself."

Accordingly, it is clear that the fact of the present case indicate that a *prima facie* case of obviousness has not been established. Thus, the apparent requirement by the Examiner of showing "unexpected results relating to obtaining the subject compound..." is not required. It is the Applicants who discovered the benefits of the present claims and the process by which it is obtained. It is the Applicants that discovered the need fur such "purification" and a method for achieving it.

However, in the interest in expediting an allowance, a Rule 132 Declaration is attached, and the superior and unexpected properties of the claimed composition are discussed. More specifically, the attached Declaration discusses the superior and unexpected differences between the present invention and the cited prior art, as well as the superior and unexpected differences between the present invention and commercially available products.

The Declaration addresses the statement in the Office Action that "applicant has not provided any evidence in verified form showing that the references' [Michel et al., US '789 and Tang '375] purification process would not result in a product having the claimed purity levels." It reinforces what is clear from the record: the "purification" descriptions relied upon in the Office Action could not confirm the presence of, or lack of, the harmful polyene/endotoxin contaminants addressed by the present invention.

Additionally, the Declaration addresses the request in the Office Action for a showing of "unexpected results relating to obtaining the subject compound having the claimed purity levels" by providing evidence that the claimed subject compositions, having the claimed purity levels, the claimed compounds are superior, as an unexpected result.

Accordingly, Applicants respectfully submit that each issue precluding allowance has been adequately addressed.

In view of the above, Applicants request that this rejection be withdrawn.

Finally, please contact the undersigned if there are any questions regarding this Amendment or the application in general.

Respectfully submitted,

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